REMARKS

In response to the final Office Action mailed April 15, 2009, Applicants respectfully request favorable reconsideration in view of the following remarks and the Rule 1.132 Declaration by Takefumi Ishidao submitted herewith. Applicants appreciate the courtesy shown by the Examiner in discussing this case with Applicants' representative on July 13, 2009. The discussions of the interview are reflected in the following remarks.

Claims 1, 3 and 9 have been amended. The amendment to claims 1 and 9 is supported by the original disclosure, for example by page 15, line 10 and page 18, lines 24-35. The amendment to claim 3 is supported by the original disclosure, for example by page 15, lines 6-7. No new matter has been added. Claims 1-17 are pending.

Claim rejections - 35 U.S.C. § 103

Claims 1-7 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP 0971039) in view of Notomi et al. (Nucleic Acids Research 2000; 28(12): e63) and further in view of Nagamine (Molecular and Cellular Probes (June 2002) 16(3):223-229). Applicants respectfully traverse the rejection.

Claims 1 and 9 recite that (X-Y)/X is in the range of -1.00 to 0.75, and that (X+Y) is in the range of 30 to 50. Claims 1 and 9 further recite that {X-(Y-Y')}/X is in the range of -1.00 to 0.75, and (X+Y+Y') is in the range of 30 to 50. Claims 1 and 9 further recite that steps (a), (b) and (c) are carried out in an isothermal condition. The primers that satisfy the above ranges as recited in claims 1 and 9 provide highly specific amplification in a short period of time in an isothermal condition as shown in the following table that includes the experimental results of Examples 1, 2 and 3 of the present specification. For example, as shown in Table A, when the sY153 STS marker was amplified with primers that satisfy the above conditions as recited in claims 1 and 9, highly specific and efficient amplification was obtained (see primer set nos. 4-11). On the other hand, where primers that do not satisfy the above conditions were used, inferior results were obtained (see primer set nos. 1-3).

[Table A]

Target	Primer	X	Y	X-Y/X	X+Y	Amplification Time(min)	Primer Set No.	Example or Comparative Example
SY153	1	20	–	–	–	Nonspecific amplification	1	Comparative Example
	2	20	–	–	–			
	3	20	0	1	20	60	2	Comparative Example
	4	20	0	1	20			
	5	20	5	0.75	25	60	3	Comparative Example
	6	20	5	0.75	25			
	7	20	10	0.5	30	40	4	Example
	8	20	10	0.5	30			
	9	20	15	0.25	35	20	5	Example
	10	20	15	0.25	35			
	11	20	20	0	40	40	6	Example
	12	20	20	0	40			
	13	20	20	0	40	40	7	Example
	14	20	20	0	40			
	15	20	20	0	40	40	8	Example
	16	20	20	0	40			
	17	20	20	0	40	40	9	Example
	18	20	20	0	40			
	19	20	20	0	40	40	10	Example
	20	20	20	0	40			
	21	20	20	0	40	40	11	Example
	22	20	20	0	40			
SY160	23	20	26	−0.3	46	90	12	Example
	24	20	20	0	40			
	25	20	26	−0.3	46	90	13	Example
	26	20	20	0	40			
M13	27	24	50	−1.08	74	Nonspecific amplification	14	Comparative Example
	28	22	53	−1.41	75			
	29	24	0	1	24	90	15	Comparative Example
	30	22	0	1	22			
	31	24	6	0.75	30	60	16	Example
	32	22	6	0.73	28			
	33	24	12	0.55	36	60	17	Example
	34	22	12	0.45	34			
	35	24	18	0.25	42	40	18	Example
	36	22	18	0.18	40			
	37	24	22	0.08	46	60	19	Example
	38	22	22	0	44			
	39	24	22	0.08	46	60	20	Example
	40	22	22	0	44			

The rejection recognizes that the use of the sY153 primers as described in the above table results in an increase in amplification efficiency, but contends that the use of the sY160 primers does not appear to show this effect. Applicants submit herewith a second Rule §1.132 Declaration by Mr. Takefumi Ishidao to show that the use of sY160 primers that satisfy the conditions as recited in claims 1 and 9 permit increased amplification efficiency. In particular, the Declaration provides comparative experiments to demonstrate the effects of sY160 primers that satisfy the conditions of $-1.00 \leq (X-Y)/X \leq 0.75$ and $30 \leq X+Y \leq 50$ as recited in claims 1 and 9.

Briefly, primers were prepared as described on pages 2-5 of the Declaration. A summary of the prepared primers is provided in Tables 1, 2 and 3 below. As shown in the tables, the primers in primer sets 1, 5 and 9 satisfy the conditions of $-1.00 \leq (X-Y)/X \leq 0.75$ and $30 \leq X+Y \leq 50$ as recited in claims 1 and 9 while primer sets 2-4 and 6-8 do not satisfy the above conditions as recited in claims 1 and 9. In the tables, Formula 1 is $-1.00 \leq (X-Y)/X \leq 0.75$ and Formula 2 is $30 \leq X+Y \leq 50$.

[Table 1]

Primer Set	Primer	Formula	X and Y	(X-Y)/X	X+Y
1	SY160LP13	1 : o 2 : o	X=20, Y=26	-0.3	46
	SY160RP13		X=20, Y=20	0	40
2	SY160LP13-1	1 : o 2 : ×	X=20, Y=5	0.75	25
	SY160RP13-1		X=20, Y=9	0.55	29
3	SY160LP13-2	1 : × 2 : o	X=15, Y=35	-1.333	50
	SY160RP13-2		X=15, Y=35	-1.333	50
4	SY160LP13-3	1 : × 2 : ×	X=20, Y=56	-1.8	76
	SY160RP13-3		X=20, Y=56	-1.8	76

[Table 2]

Primer Set	Primer	Formula	X and Y	(X-Y)/X	X+Y
5	SY160LP16	1 : o 2 : o	X=20, Y=26	-0.3	46
	SY160RP16		X=20, Y=20	0	40
6	SY160LP16-1	1 : o 2 : ×	X=20, Y=33	-0.65	53
	SY160RP16-1		X=20, Y=9	0.55	29
7	SY160LP16-2	1 : × 2 : o	X=15, Y=35	-1.333	50
	SY160RP16-2		X=15, Y=33	-1.2	48
8	SY160LP16-3	1 : × 2 : ×	X=20, Y=51	-1.55	71
	SY160RP16-3		X=20, Y=45	-1.25	65

[Table 3]

Primer Set	Primer	Formula	X and Y	(X-Y)/X	X+Y
9	SY160 TP-F(16,32)	1 : o 2 : o	X=16, Y=32	-1	48
	SY160 TP-R(16,32)		X=16, Y=32	-1	48

The above primers were then used to amplify the sY160 STS marker using Human DNA as template under isothermal conditions. The amplification results are shown in Figs. 2-3 and 6 attached to the Declaration.

As shown in lanes 2-5 in Fig. 2 (primer set 1), lanes 3-5 in Fig. 3 (primer set 5) and lane 2 of Fig. 6 (primer set 9), when primer sets 1, 5 and 9 satisfying the conditions of $-1.00 \leq (X-Y)/X \leq 0.75$ and $30 \leq X+Y \leq 50$ as recited in claims 1 and 9 were used, the targeted amplification product (about 260 base pairs) was obtained in a reaction time as short as 90 minutes after the template was added.

In order to determine the specificity of the amplification, the amplified products using primer sets 1, 5 and 9 were treated with a restriction enzyme and the cleaved products were analyzed for the expected change in sizes of the product. The expected change in sizes of the targeted product was obtained as shown in the restriction enzyme digest results in lane 2 in Fig. 4 (primer set 1), lane 2 in Fig. 5 (primer set 5) and lane 3 in Fig. 6 (primer set 9), thereby verifying that the desired amplified product was amplified when using primer sets 1, 5 and 9.

On the other hand, when primer sets 2-4 and 6-8 which do not satisfy the conditions of $-1.00 \leq (X-Y)/X \leq 0.75$ and $30 \leq X+Y \leq 50$ as recited in claims 1 and 9 were used, the desired product was not obtained. Specifically, primer set 2 gave products after 90 minutes (lanes 8-10 of Fig. 2), but none of the products obtained were specific to sY160 (see restriction digest results for primer set 2 in lane 3 of Fig. 4).

Similarly, primer sets 6 and 8 gave products after 150 minutes (lane 15 in Fig. 2, lane 10 and lane 21 in Fig.3, respectively), but none of the products obtained were specific to the targeted marker (see restriction digest results for primer set 6 in lane 10 in Fig. 3 and primer set 8 in lane 21 in Fig. 3).

Primer set 3 gave amplified products, but only after 150 minutes (lane 15 in Fig. 2). When primer set 4 was used, no amplified product was obtained even after 150 minutes of reaction time.

From the experimental data provided in the Declaration and the discussion above, it is clear that increased amplification efficiency can be obtained when primers that satisfy the conditions as recited in claims 1 and 9 are used to amplify the sY160 STS marker. Accordingly, Applicants respectfully submit that the showing of unexpected results is commensurate in scope with the claims.

The rejection further contends that the data in Table A does not clearly establish that an increase in amplification efficiency is correlated with X+Y and X-Y/X values within the claimed ranges. Specifically, the rejection contends that primer set nos. 2, 3 and 16 have X+Y and X-Y/X values that lie outside of the claimed ranges, but show amplification efficiencies that are similar to those obtained with primer set no. 17, which has an X+Y and X-Y/X value within the claimed ranges. However, primer set nos. 2 and 3 are primers that were used to amplify the sY153 STS marker using human DNA as a template, whereas primer set nos. 16 and 17 are primers that were used to amplify the M13mp18RF vector using the same DNA as a template. The targeted product and the template used are completely different for primer set nos. 2 and 3 and primer set nos. 16 and 17, and thus, there is no reason to compare the results of primer set nos. 2 and 3 and primer set nos. 16 and 17.

As shown in Table A, primer set nos. 14-20 were used for the amplification of the M13mp18RF vector. Primer set nos. 14 and 15 are those that do not satisfy the claimed ranges of X+Y and X-Y/X, whereas primer set nos. 16-20 are those that satisfy the claimed ranges of X+Y and X-Y/X. Primer set no. 14 showed non-specific amplification and primer set no. 15 showed amplification of the targeted product only after 90 minutes. On the other hand, primer set nos. 16-20 showed increased amplification efficiency as compared to primer set nos. 14 and 15. Accordingly, Applicants submit that the data shown in Table A and in the Declaration submitted herewith clearly establish a nexus between amplification efficiency and the claimed X+Y and X-Y/X values.

The rejection further contends that Notomi only teaches that the parameters should be optimized and does not actively disparage, discredit or discourage the use of other lengths for the regions corresponding to the X and Y values. However, Notomi provides results showing a strict requirement for recognition of six distinct sequences in the target DNA in LAMP (see Fig. 4B, lanes 2-4), thereby leading away from applying their primer design to that of Rabbani, which does not involve six distinct sequences. Nagamine is an improvement on Notomi's design,

where two additional distinct sequences are used. Both Notomi and Nagamine's amplification system involve completely different mechanisms from Rabbani's amplification system. Therefore, Applicants respectfully submit that there is no reasonable basis for combining the references. Accordingly, claims 1 and 9 and the dependent claims therefrom are patentable over the references for at least these reasons.

Claims 8 and 17 are rejected under 35 USC 103(a) as being unpatentable over Rabbani et al. in view of Notomi et al., further in view of Nagamine (Molecular and Cellular Probes (June 2002) 16(3):223-229) and further in view of Kool, E.T. (Current Opinions in Chemical Biology (2000) 4: 602-608). Applicants respectfully traverse the rejection.

Rabbani, Notomi and Nagamine have been distinguished above. Kool does not remedy the deficiencies of Rabbani, Notomi and Nagamine. Therefore, claims 8 and 17 are patentable over the references taken alone or together. Applicants do not concede the correctness of the rejection.

Favorable reconsideration and withdrawal of the rejection are respectfully requested.

In view of the foregoing, favorable reconsideration in the form of a notice of allowance is requested. Any questions or concerns regarding this communication can be directed to the attorney-of-record, Douglas P. Mueller, Reg. No. 30,300, at (612) 455.3804.

Respectfully submitted,

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